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NUCLEOPHILIC ADDITION OF HYDROGEN SULFIDE AND THIOLS TO DIACETYLENE ALCOHOLS AND DIOLS

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The synthesis of thiophene compounds, alkylthioenyne alcohols and glycols are discussed.

Keywords: Thiylation; liquid ammonia; thiophene alcohols and glycols; diacetylene alcohols, glycols; alkylthioenyne alcohols, glycols; thiols

CONTENTS

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1. INTRODUCTION

Diacetylene (DA) functional derivatives represent a large group of natural compounds which play an essential role in the life of plants.[1] The reactivity of these compounds arouses an interest and is of great importance in the investigation of natural poly-yne biogenesis. Owing to their high reactivity and availability,[2-5] DA alcohols and glycols provide convenient starting materials for the creation of new fungicides,[6] drugs,[7] polymeric materials,[8,9] functionally-substituted heterocyclic and unsaturated compounds.[10]

The data concerning thiylation of disubstituted DA homologs[11-13] and DA alcohols,[14] presented in the monograph by Shostakovsky and Bogdanova,[2] are now aged and need to be updated.

2. REGULARITIES OF NUCLEOPHILIC ADDITION TO THE DIYNE SYSTEM

Thiolate-ion attack may occur at a triple bond depending on the conjugated system polarity under inductive effects of substituents or steric requirements.[11]

In order to establish the electron-deficient centers in diynes and to explain the directions of RS^- nucleophilic addition to diynes, Volkov *et al.*[15] made use of ^{13}C NMR spectra, since ^{13}C chemical shifts (CS) are known to mainly reflect the charge density on carbon atoms. Table I shows ^{13}C NMR CS of a series of diacetylenes.

As seen from Table I, the 1-hydroxyisopropyl group (alcohol **5**) exerts a deshielding effect on C^1 and C^4 carbon atoms. The phenyl substituent (diyne **3**) also deshields these carbon atoms and, besides, deshields slightly C^2 whereas the methyl group (compound **1**) shields C^2 and slightly deshields C^1. In alcohols **8** and **11** the effects of these substituents are nearly of additive character: ^{13}C CS of acetylene hydrocarbons can

TABLE I ^{13}C CS (δ, ppm) of diynes.[15] $R^1-C^1\equiv C^2-C^3\equiv C^4-R^2$ (40% solution in cyclohexane)

Diyne	R^1	R^2	C^1	C^2	C^3	C^4
DA	H	H	64.5	68.2	68.2	64.5
1	Me	H	73.6	64.7	69.0	64.0
2	*t*-Bu	H	85.0	64.2	68.8	65.8
3	Ph	H	75.1	74.0	68.4	70.9
4	$HOCH_2$	H	74.7	69.7	67.5	68.8
5	$(Me)_2COH$	H	81.1	66.7	67.8	69.3
6	$(Et)_2NCH_2$	H	73.3	69.3	68.3	66.8
7	Me	$HOCH_2$	77.7	64.4	70.4	77.6
8	Me	$(Me)_2COH$	76.9	64.3	67.5	79.8
9	*t*-Bu	$(Me)_2COH$	84.3	66.0	67.8	89.5
10	Ph	$HOCH_2$	82.5	73.6	69.6	78.1
11	Ph	$(Me)_2COH$	79.1	74.6	67.9	87.9
12	$MeOCH_2$	$(Me)_2COH$	75.9	70.8	66.0	84.7
13	$HOCH_2$	$HOCH_2$	78.6	68.7	68.7	78.6
14	$HOCH_2$	$(Me)_2COH$	78.3	69.1	66.2	83.7
15	MeCHOH	$(Me)_2COH$	82.1	67.7	66.2	84.4
16	$(Me)_2COH$	$(Me)_2COH$	85.3	65.8	65.8	85.3

be fairly well predicted based on the CS of the corresponding mono-substituted DA.[15,17]

The results of the use of ^{13}C CS changes in alcohols **8** and **11** for finding the most electron-deficient atoms allows a suggestion[17] that in alcohol **11** the nucleophile may add to the C^1-C^4 atoms showing a predisposition to C^4 due to a higher polarity of the $C^3\equiv C^4$ bond. Replacement of the phenyl radical by a methyl one (alcohol **8**) considerably changes the charge density distribution; the difference in triple bond polarity becomes nearly equal, the C^1 and C^4 electron-deficiency is reduced and, consequently, nucleophile attack at these sites is less favored. In this case steric factors are of greater importance and nucleophilic attack involves the least sterically hindered carbon atom C^1. In glycols **13** and **16** the triple bonds are equivalent and the nucleophile adds to C^1 and C^4 to form compounds having a single structure.

It is known[2] that independent of the electronic nature of the substituent, mono-substituted DA add thiolate-ion mainly at a mono-substituted triple bond in the same direction as with unsubstituted DA. The nucleophilic addition of thiol to the terminal acetylenic bond is found to occur against the Markovnikov rule to form unsaturated sulfides of *Z*-configuration. The direction of nucleophile attack at the

unsubstituted DA triple bond is not always in agreement with the electron density distribution in these hydrocarbons (Table I), since the terminal carbon atom bears the highest negative charge.[18]

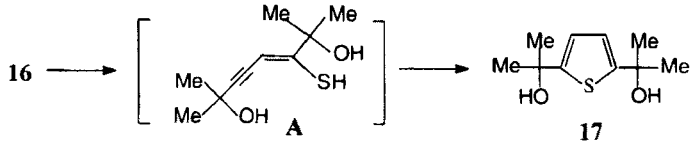
3. ADDITION OF HYDROGEN SULFIDE TO DIACETYLENE ALCOHOLS AND DIOLS

A synthetic route to compounds of the thiophene series reported by Schulte *et al.*[19-21] was often used for the synthesis of natural sulfur-containing compounds.[22-25] Cysteine and glutathione, which abstract hydrogen sulfide in the presence of alkalis, can serve as H_2S donors. Thus, for example, in the presence of glutathione at 20 °C a natural compound *E*-7-phenyl-2-heptene-4,6-diyn-1-ol readily transforms in 0.1 N KOH to the corresponding thiophene in good yield.[19]

It is quite evident, however, that reactions making a direct use of hydrogen sulfide or sodium sulfide are of practical value. The above reaction was employed by many chemists for the synthesis of phenyl[26,27] and phenylferrocenyl ether,[28] glycols[29-31] and amines[32] of the thiophene series.

Special attention was given to the synthesis of tertiary hydroxy-containing thiophenes[29,30] transformed with dehydrating agents to unsaturated compounds among which thiophene analogs of styrene, methylstyrene and divinylbenzene were of most interest.

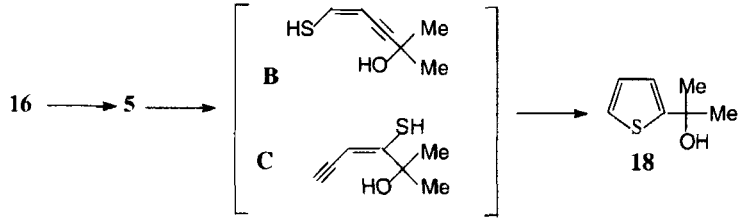
Glycol **16** was shown[25] to add hydrogen sulfide in the presence of alkali to form thiophene glycol **17** in 37% yield (Scheme 1).



SCHEME 1

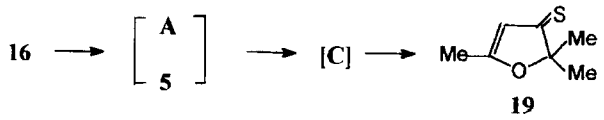
In the presence of a significant amount of alkali (30%) the yield of thiophene compounds can be increased to 50%.[29] In this case, along with thiophene glycol **17** it was possible to isolate a crystalline compound to which the thiophene alcohol **18** structure was tentatively ascribed. The formation of the alcohol is readily explained in terms of cleavage of glycol **16** (retro-Favorsky reaction) to DA alcohol **5** which

leads to thiophene alcohol **18** in the reaction with hydrogen sulfide via intermediates **B** or **C** (Scheme 2).



SCHEME 2

Further study has shown the isolated compound to be a member of a new class of compounds, 2,2,5-trimethyl-2,3-dihydrofuran-3-thione **19**. This reaction can follow a scheme of hydrogen sulfide addition to glycol **16** to form the intermediate compound **A** which mainly undergoes cyclization to thiophene glycol **17**. At the same time, the formation of alcohol **5** and partial involvement of compound **A** in the retro-Favorsky reaction to afford an intermediate alcohol **C** which contributes to intramolecular cyclization (not typical of this reaction) of the hydroxyl group to form substituted dihydrofuranthione **19** seem quite possible (Scheme 3).



SCHEME 3

Under analogous conditions the alcohol **5** also reacts with hydrogen sulfide to form a mixture of products consisting of thiophene alcohol **18** and dihydrofuranthione **19** in a yield ranging from 5% to 12% depending on the reaction temperatures, i.e., the same competition of the hydroxy and thiol groups is observed. If compound **18** forms in fact via the intermediate alcohol **C**, this indicates an unusual addition of thiolate-ion at the disubstituted triple bond of the alcohol **5** rather than at its terminal triple bond. This is consistent with the data of the alcohol **5** thiylation (see Section 4).

In the IR spectrum of compound **19** there are no absorption bands corresponding to the hydroxy group and thiophene ring.

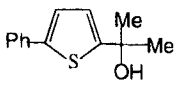
The absorption band at 1530 cm^{-1} is assigned to the =CH–S fragment, whereas the bands at 1619 and 2540 cm^{-1} are related to the terminal triple bond and mercapto group, respectively.

The ^1H NMR spectrum of compound **19** displays a singlet (δ 1.4 ppm) corresponding to two geminal methyl groups, a singlet (δ 2.2 ppm) arising from the methyl group located at the ring double bond, and a low-field singlet (δ 6.0 ppm) related to the double bond proton.

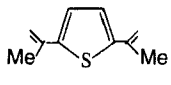
Thione–thiol tautomerism was proved by potentiometric titration of compound **19** in pyridine (0.1 N alcohol KOH solution).

Thiophene alcohol **20** was obtained in 47% yield from alcohol **11** and hydrogen sulfide in an analogous pathway.

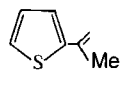
2,5-Diisopropenylthiophene **21**, 2-isopropenylthiophene **22** and 2-isopropenyl-5-phenylthiophene **23** were obtained by dehydrogenation of glycol **17** and alcohols **18**, **20** in the presence of acetic, oxalic acids or potassium bisulfate, respectively, in 78%, 72% and 80% yield.[30]



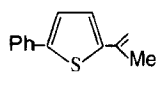
20



21



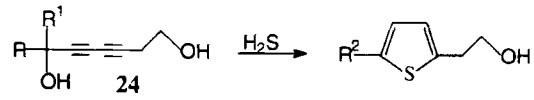
22



23

The structure of compounds **21–23** was proved by IR and ^1H NMR spectra. These unsaturated thiophene compounds polymerize readily at elevated temperature. Thus, from the thiophene **21** at 170 °C a glass-like polymer insoluble in ether, benzene, alcohol, acetone and hexane was prepared. On the basis of thiophene **21** a process for the preparation of sulfopolystyrene cation-exchangers distinguished by an enhanced swelling capacity and chemical resistance has been developed.[33]

A reaction of unsymmetrical DA glycols **24** with hydrogen sulfide in the presence of sodium thiolate in boiling toluene was performed.[31] Instead of the expected 2,5-dihydroxyalkylthiophenes the products of their dehydration at the expense of OH tertiary group, 5-(2-hydroxyethyl)-2-alkylthiophenes **25** were obtained (yields 67% and 47%). No expected result was achieved either when the reaction was carried out in an autoclave with sodium hydrosulfide in acetone (100 °C) or upon the action of hydrogen sulfide in the presence of potassium methylate or *tert*-butylate or alcohol alkali (Scheme 4).



$R = R^1 = Me$, $R-R^1 = (CH_2)_5$. **25** (R^2 = Me ), **25a** ()

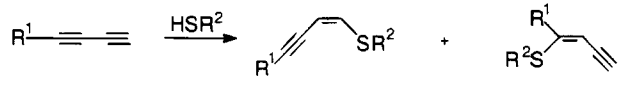
SCHEME 4

4. PREPARATION OF SULFUR-CONTAINING ENYNE ALCOHOLS AND DIOLS

4.1. Reaction of Diacetylene Alcohols with Thiols

It has been reported[34–36] that DA and mono-substituted DA derivatives are readily thiylated in liquid ammonia. The reaction proceeds under mild conditions (−33 °C) without catalysts and is completed with addition of only one equivalent of thiol to form *Z*-ethynylvinylsulfides in good yield.

Unsubstituted DA alcohols also add the thiolate-ion in liquid ammonia mainly at the mono-substituted triple bond (Scheme 5).[35]



4, 5 **26-33** **34-39**

26-31 [$R^1 = (Me)_2COH$, R^2 = Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu]; **32, 33** ($R^1 = CH_2OH$, R^2 = Et, *t*-Bu); **34-37** [$R^1 = (Me)_2COH$, R^2 = Et, *n*-Pr, *i*-Bu, *t*-Bu]; **38, 39** ($R^1 = CH_2OH$, R^2 = Et, t-Bu).

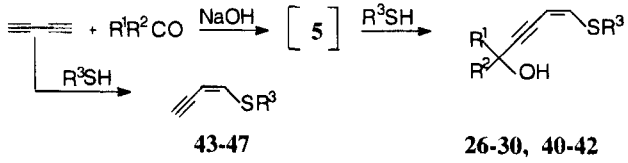
SCHEME 5

With alcohols **4** and **5** a deviation from regioselectivity is observed since the thiolate-ion attacks both C^4 and C^1 carbon atom adjacent to the hydroxyalkyl group, which is consistent with the data of Table I. In the reaction of the alcohol **4** with ethanethiol the sulfides **32** and **38** were isolated in a ratio of 1 : 1 determined from the signal integral intensities in ^{1}H NMR spectra. The replacement of ethyl radical by a more bulky *tert*-butyl radical changes to 1.5 : 1 the ratio of regio isomers **33** and **39**, which is of little significance. In going to tertiary DA alcohol **5**, steric factors may have a marked effect on the reaction course. The content of

sulfides **34** and **37** is decreased to 20% and to 15% with *tert*-butanethiol. The induction effect of the hydroxyalkyl group is thought[35] to be the main factor responsible for lack of regioselectivity in the reaction of thiols with DA alcohols, although, judging by the distance between the OH group and the reaction center the inductive effect should not be significant. It should also be mentioned that the portion of addition at the disubstituted triple bond decreases as the attacking nucleophile becomes more bulky, but steric hindrance does not affect much the reaction trans-specificity. The high regioselectivity of the process is confirmed by ^{1}H NMR spectra for compounds **26–31** and, **32** and **33** displaying two vinyl proton signals with a coupling constant of $\sim$ 10 Hz (*Z*-disposition of the substituents) and by those for compounds **34–39** having only one vinyl signal.

In contrast to alkanethiols, thiophenol reacts with the alcohol **5** only at the terminal acetylene bond to form *Z*-6-phenylthio-2-methyl-5-hexen-3-yne-2-ol.[37] The high regio- and *Z*-stereoselectivity of the process is proved by ^{1}H NMR spectrum showing two vinyl proton signals with a coupling constant of $\sim$ 10 Hz.

Based on the data obtained a simple and efficient one-pot method for the synthesis of tertiary alkylthioenyne alcohols **26–30**, **40–42** from DA, ketones and thiols in liquid ammonia has been developed (Scheme 6).[38,39]



43-47 **26-30, 40-42**

26-30 ($R^1 = R^2 = Me$, $R^3 = Et$, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu); **40** ($R^1 = Me$, $R^2 = R^3 = Et$); **41** [R^1–$R^2 = (CH_2)_4$, $R^3 = Et$]; **42** [R^1–$R^2 = (CH_2)_5$, $R^3 = Et$]; **43-47** ($R^3 = Et$, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu).

SCHEME 6

These reactions are more conveniently performed using a 10% DA solution in liquid ammonia with DA : ketone : thiol with molar ratios of 1 : 0.5 : 1.2, 1 : 0.75 : 1.2 or 1 : 1 : 1.2 in the presence of 0.1–0.01 mol of alkali metal hydroxide. The alkali metal hydroxide catalyses DA

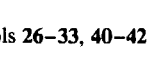
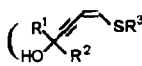
condensation with ketones and simultaneously accelerates the reaction of the intermediate alcohol **5** and residual DA with thiols. These taken in slight excess, contribute to the synthesis of tertiary alkylthioenyne alcohols **26–30** in isolated yields of 83–96%.

Excess DA over ketone is needed to orient the reaction towards the intermediate alcohol **5** and to eliminate the possibility of obtaining glycol. The yield of side *Z*-ethynylvinylsulfides **48–56** is 20–30% based on DA used. The properties of these compounds are presented in Tables II and III.

This simple synthetic route to alkylthioenyne alcohols **26–30, 40–42** opens up fresh opportunities for their use in synthetic chemistry and for the preparation of new derivatives rather promising in search for pharmacological agents.

4.2. Reaction of Substituted Diacetylene Alcohols with Thiols

The thiylation of substituted DA alcohols is performed in liquid ammonia, with or without catalytic amounts of alkali with the DA alcohol : thiol molar ratios being 1 : (1.2–1.3). This reliable procedure of thiylation of diynes leads to primary alkylthioenyne alcohols **48, 49**

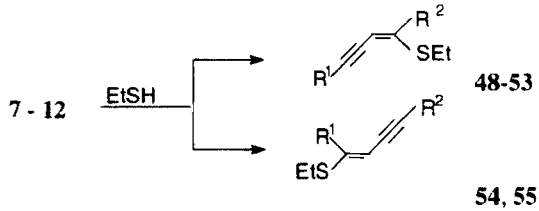
TABLE II Alcohols **26–33, 40–42**  **34–39**  [35,37–39,44]

Compound no.	R^1	R^2	R^3	*Yield*, %	*Boiling point*, °C (mmHg)	n_D^{20}	d_4^{20}
26	Me	Me	Et	82.6	93–94 (2.5)	1.5387	1.1014
27	Me	Me	*n*-Pr	90.5	100–103 (1)	1.5319	1.0044
28	Me	Me	*i*-Pr	88.8	113–115 (1)	1.5238	0.9740
29	Me	Me	*n*-Bu	86.4	116–119 (1)	1.5252	0.9685
30	Me	Me	*i*-Bu	82.5	114–117 (2)	1.5241	1.0283
31	Me	Me	*t*-Bu	75.0	89 (2)	1.5170	0.9639
32	H	H	Et	49.0	98 (3)	1.5695	
33	H	H	*t*-Bu	58.0	95–96 (2.5)	1.5365	
34	Me	Me	Et	72.0	94 (2)	1.5289	1.1009
35	Me	Me	*n*-Pr	16.0	91–92 (2)	1.5225	1.0020
36	Me	Me	*i*-Bu	18.0	67–69 (1.5)	1.5188	1.0098
37	Me	Me	*t*-Bu	13.0	88 (2)	1.5103	1.0003
38	H	H	Et	49.0	92 (2)	1.5588	
39	H	H	*t*-Bu	40.0	94 (2)	1.5283	
40	Et	Me	Et	96.0	110–113 (1)	1.5378	
41	R^1–R^2 = $(CH_2)_4$		Et	84.0	130–133 (1)	1.5625	
42	R^1–R^2 = $(CH_2)_5$		Et	88.0	131–134 (1)	1.5629	

TABLE III ^{1}H NMR spectra of alkylthioenyne alcohols **26–42**[35,37]

Compound no.	*CS*, δ, ppm, *CDCl*$_3$							
	Me	SCH_2	*=CHS*	*=CH*	*≡CH*	*Me*	$(Me)_2$	OCH_2
26	1.30t	2.74q	6.30d	5.43q			1.44s	
27		2.69t	6.30d	5.38q		1.00t	1.44s	
28	3.08t (SH)		6.36d	5.36d		1.30d	1.50s	
29		2.66t	6.27d	5.32d		0.87t	1.45s	
30		2.61d	6.27d	5.32d		0.97d	1.45s	
31			6.45d	5.38d		1.32s	1.45s	
32	1.32t	2.75q	6.34d	5.43d				4.31d
33			6.52d	5.30d		1.40s		4.35d
34	1.22t	3.06q		6.17q	3.25q		1.35s	
35		3.00t		6.15q	3.20q	1.00t	1.35s	
36		2.91q		6.07q	3.15q	1.02q	1.33s	
37				6.30q	3.15q	1.53s	1.40s	
38	1.27t	2.92q		5.76m	3.15q			4.16d
39				6.30m	3.05q	1.40s		4.17d
40	1.26t	2.72q	6.30d	5.40d			1.33d	4.50q (OCH)
41	1.28t	2.69q	6.34d	5.37d				
42	1.30t	2.77q	6.30d	5.38d				

and tertiary alcohols **50–53** in 81–95% and 75–96% yield, respectively (Scheme 7).[40]



48, 54 (R^1 = Me, R^2 = CH_2OH); **49** (R^1 = Ph, R^2 = CH_2OH);

50 [R^1 = Me, R^2 = $(Me)_2COH$]; **51, 55** [R^1 = CH_2OMe, R^2 = $(Me)_2COH$]

52 [R^1 = *t*-Bu, R^2 = $(Me)_2COH$]; **53** [R^1 = Ph, R^2 = $(Me)_2COH$].

SCHEME 7

As the initial alcohols **7–11** contain two conjugated triple bonds, the addition of thiols can be expected to result in the formation of four alternative structures (each in the *Z*- and *E*-forms). However, taking into account the effect of substituents and having the ^{13}C NMR spectra of these alcohols available for determining the most electron-deficient

carbon atoms of the diyne chain (Table I) one can assert the C^1 and C^4 electrophilic centers to be the most probable sites of the thiolate ion attack.[16] This leads to the formation of alkylthioenyne alcohols **48–53** and, **54** and **55** of either *E*- or *Z*-configuration. Variation of the R^1 substituents in the initial alcohols from Me to Ph brings about a change in the diyne chain electron density and triple bond polarity (Table I), which is reflected in the reactivity and governs the nucleophile attack direction.

Primary alcohol **10** (R = Ph) is readily thiylated in liquid ammonia for 5 h in the absence of catalyst to give enyne alcohol **49** in practically quantitative yield. Tertiary alcohol **11** undergoes thiylation under the same conditions (−33 °C, 2.5–4.5 h) or directly in a medium of thiol (KOH, 80 °C, 14 h). Alcohols with a methyl substituent **7** and **8** (especially, **8**) are slowly thiylated in liquid ammonia in the presence of an alkaline agent. Therefore, it is more convenient to carry out the reaction in pyridine (NaOH, 20 °C, 6 h) or in thiol (KOH, 110 °C, 14 h). The addition of thiol to tertiary alcohol having a *tert*-butyl substituent **9** could be performed only in a methanol medium (KOH, 75 °C, 13 h).[40]

In general, as should be expected, alcohols containing electron-donating substituents (R^1 = Me, *t*-Bu) undergo thiylation under more rigid conditions than alcohols with an electron-withdrawing substituent, which is also in agreement with the data of ^{13}C NMR spectra analysis (Table I).

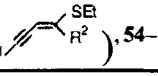
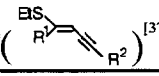
Thus, the determination of electron-deficient centers using ^{13}C NMR spectroscopy allows a reliable prediction of the nucleophile attack site in disubstituted diyne, which is essential in designing compounds of present structure.

As follows from, Ref. [40] the interaction of thiols with the alcohols **8–11** occurs exclusively (and predominantly with the alcohol **7**) at the C^4 electrophilic center with the observance of the *trans*-addition rule. With the alcohol **12** the reaction is not regioselective and the thiolate-ion attacks both C^1 and C^4 carbon atoms to form the adducts **51** and **55** in the 1 : 1 ratio. The assignment of structures **51** and **55** was made based on the coupling constants in the ^1H NMR spectrum, which displayed two signals corresponding to the olefin proton and the OCH_2 group ($^4J_{HCH_2O} \sim 1$ Hz, $^5J_{HCH_2O} \sim 2$ Hz). The addition of thiol at the $C^3 \equiv C^4$ bond of tertiary alcohols **8**, **9** and **11** is indirectly confirmed by the fact that the adducts obtained undergo no cleavage under the conditions of

retro-Favorsky reaction, i.e., they are not tertiary alcohols. Moreover, in the IR spectra of compounds **49**, **50**, **52** and **53** recorded in a CCl_4, solution at 0.01 and 0.002 mol/l concentrations two absorption bands corresponding to non-associated and associated hydroxy groups are clearly defined at 3615 and 3540 cm^{-1}, respectively. The band at 3540 cm^{-1} indicates the presence in these compounds of an intramolecular hydrogen bond which, in turn, points to a 1,2-array of the thioalkyl and hydroxyl groups.[41]

The structures of the thiol 3,4-addition products to alcohols **7–12** were based on additive scheme calculations of CS values (δ, ppm) of the ethylene proton for *Z*- and *E*-configurations and from comparisons with the experimental data as well as on coupling constants. Thus, for example, for the *Z*-configuration of compound **48** the olefinic proton hydroxymethyl groups allyl coupling is approximately 1.5 Hz, thus indicating their *Z*-array, whereas for the *E*-structure this constant should be about 0.8 Hz. The thiophenol adds to tertiary alcohol **11** in liquid ammonia in the presence of alkali in an analogous manner, i.e., adjacent to the hydroxyisopropyl group. The structure of compound **56**, 3-phenyl-2-methyl-6-phenyl-3-hexen-5-in-2-ol is proved by ^1H NMR spectrum and by the fact that the compound undergoes no cleavage under the conditions of the retro-Favorsky reaction.

Thus, the direction of thiolate-ion addition to the diyne system of substituted DA alcohols **7–12** is governed by the substituent electron nature, i.e. by the triple bond polarity. The properties and ^1H NMR spectra of alkylthioenyne alcohols **48–56** are presented in Tables IV and V.

TABLE IV Substituted alcohols **48–53**  , **54–56**  [37,40]

Compound no.	R^1	R^2	*Yield,* %	*Boiling point* (mmHg)	n_D^{20}
48	Me	CH_2OH	81.0	108–109 (2)	1.5672
49	Ph	CH_2OH	95.0	160–162 (2)	1.6496
50	Me	$C(Me)_2OH$	75.0	110–112 (4)	1.5365
51	$MeOCH_2$	$C(Me)_2OH$	45.0	124–126 (1.5)	1.5311
52	*t*-Bu	$C(Me)_2OH$	88.0	43–45 (M.p.)	
53	Ph	$C(Me)_2OH$	96.0	59–60 (M.p.)	
54	Me	CH_2OH	15.0	108–109 (2)	1.5685
55	$MeOCH_2$	$C(Me)_2OH$	45.0	124–126 (1.5)	1.5325
56	Ph	$C(Me)_2OH$	99.0	140–142 (1)	1.6440

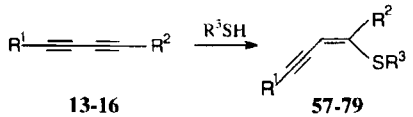
TABLE V ^{1}H NMR spectra of substituted alkylthioenyne alcohols **48–56**[37,40]

Compound no.	*CS*, δ, ppm, *CDCl*$_3$						
	(Me)$_2$	*Me in Et*	*SCH*$_2$	*=CH*	*OCH*$_2$	*OMe*	*Me*
48		1.25t	2.89q	5.71m	4.12d		2.00d
49		1.25t	2.93q	5.98t	4.19d		
50	1.33s	1.21t	2.98q	6.10q			1.98d
51	1.35s	1.23t	2.91q	5.67q	3.97d	3.26s	
52	1.31s	1.10t	3.01q	6.08s			1.25s $(Me)_3C$
53	1.37s	1.26t	3.10q	6.35s			
54		1.25t	2.89q	5.37m	4.32d		2.00d
55	1.45s	1.23t	3.02q	6.23t	4.21d	3.35s	
56	1.35s		7.20s (PhS)	6.45s			

4.3. Reaction of Symmetrical and Unsymmetrical Diacetylene Diols with Thiols

Volkov *et al.* were the first to study the regio-stereochemistry of the nucleophilic thiylation reaction of symmetrical and unsymmetrical DA glycols **13–16** in a wide range of solvents.[17,42] The synthesis of symmetrical and unsymmetrical alkylthioenyne glycols **57–79** was found to occur readily in the reaction of glycols **13–16** with thiols in the presence of catalytic amounts of alkalis in a medium of ammonia or organic solvent. The reaction of 2,4-hexadiyne-1,6-diol **13** with alkanethiols in liquid ammonia performed without catalyst by simple stirring the reagents for 2–3 h at the ammonia boiling point (−33 °C) and the hexadiyne : thiol molar ratio equal to 1 : (1–1.3). The end products yields are 90–98%. With other glycols the reaction is better carried out in liquid ammonia in the glycol : thiol : alkali ratio of 1 : (1–2) : 0.2 (Table VI), which enables the isolation of glycols **57–79** in nearly quantitative yield (89–99%). In the initial glycols **13–16** the hydroxymethyl, hydroxyethyl and hydroxyisopropyl groups slightly decrease the electron density on the C^1–C^4 atoms of the conjugated DA tylene system (Table I). That is why in the thiylation of symmetrical glycols **13** and **16** the triple bonds are of similar value and the thiol adds to the C^1 or C^4 atoms with the formation of only one product **57–65** and **72–75** (Scheme 8).

The introduction of a thioalkyl group into the above sulfides results in electron density redistribution, which impedes the electrophilic addition of a second thiol molecule under mild conditions (Table VI).



13-16 **57-79**

57-65 ($R^1 = R^2 = CH_2OH$, R^3 = Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu, C_6H_{13}, C_8H_{17}, Ph); **66** (R^1 = MeCHOH, $R^2 = CH_2OH$, R^3 = Et); **67** ($R^1 = CH_2OH$, R^2 = MeCHOH, R^3 = Et); **68** [$R^1 = (Me)_2COH$, $R^2 = CH_2OH$, R^3 = Et]; **69** [$R^1 = CH_2OH$, $R^2 = (Me)_2COH$, R^3 = Et]; **70** [$R^1 = (Me)_2COH$, R^2 = MeCHOH, R^3 = Et]; **71** [R^1 = MeCHOH, $R^2 = (Me)_2COH$, R^3 = Et]; **72-77** [$R^1 = R^2 = (Me)_2COH$, R^3 = Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, Ph]; **78** [$R^1 = R^2$ = Et(Me)COH, R^3 = Et]; **79** [R^1–$R^2 = (CH_2)_4COH$, R^3 = Et].

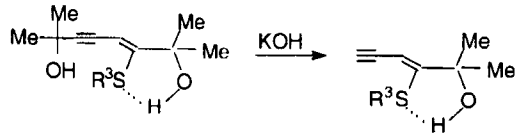
SCHEME 8

TABLE VI Effect of the reaction conditions on the yield of alkylthioenyne glycols **57**, **58**, **63**, **68**, **70**, **72**, **73**, **75–77**, **79**[17,42]

Compound no.	*Glycol*, mol	*Thiol*, mol	*NaOH*, mmol	*Solvent*	*V*, ml	*T*, °C	*Time*, h	*Yield*, %
57	0.014	0.016		Liq. NH_3	70	−33	2.5	98
58	0.009	0.011		Liq. NH_3	45	−33	2.5	95
63	0.004	0.005	1.3	Liq. NH_3	50	−33	5	90
68	0.017	0.021	1.3	Liq. NH_3	70	−33	5	98
70	0.015	0.018	6.0	Liq. NH_3	75	−33	5	99
72	0.012	0.020	2.5	Liq. NH_3	80	−33	4	94
72	0.006	0.013	0.7	Pyridine	10	15–20	3	96
72	0.006	0.013	0.7	DMSO	10	15–20	3	90
72	0.006	0.013	0.7	MP*	10	15–20	3	94
72	0.006	0.013	0.7	MP	10	25–30	5	76
73	0.012	0.024	2.5	Liq. NH_3	90	−33	5	95
73	0.006	0.013	0.7	Pyridine	10	20–25	4	95
75	0.012	0.024	2.5	Liq. NH_3	85	−33	7	89
75	0.006	0.013	0.7	DMSO	8	15–20	3	94
75	0.006	0.013	1.3	MeOH	10	64–66	13	91
76	0.012	0.024	2.5	Liq. NH_3	85	−33	8	95
76	0.006	0.013	0.7	DMF	10	15–20	3	96
77	0.012	0.012	2.5	Liq. NH_3	95	−33	5	95
79	0.009	0.011	2.5	Liq. NH_3	180	−33	5	96

*MP – N-methylpyrrolidone.

The structure of glycols **72**, **73** and **76** was unambiguously proved by the retro-Favorsky reaction. The only reaction products are alcohols **34–36** corresponding in their chemico-physical properties to the alcohols prepared by carbinol **5** thiylation (Scheme 9).



72, 73, 76 **34-36**

SCHEME 9

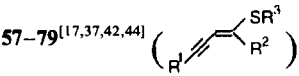
In the IR spectra of alcohols **34–36** run in 0.01 and 0.002 mol/l CCl_4 solutions two absorption bands corresponding to unassociated and associated OH groups (3615 and 3540 cm^{-1}, respectively) are clearly defined. The band at 3540 cm^{-1}, is indicative of the intramolecular hydrogen bond present in these compounds.[17]

With unsymmetrical DA glycols **14** and **15** the thiol can add to the C^1 and C^4 atoms of the diyne chain. As seen from Table I, the C^4 atom adjacent to the hydroxyisopropyl group is the most electron-deficient atom. In this case, however, steric factors should be of importance. Therefore, the nucleophilic attack may be directed to the other, less sterically hindered electrophilic center (C^1). The glycols **14** and **15** turned out to be attacked by the thiolate-ion at both C^1 and C^4 atoms. This means that the reaction follows not a regioselective pathway. The ^1H NMR spectra of compounds **66**, **68** and **70** display two vinyl proton signals (in a 1.5 : 1 ratio), subjected to coupling constant-based structural assignment.[17]

The reaction of symmetrical glycols **13** and **16** with thiophenol in liquid ammonia affords exclusively enyne glycols **65** and **77**. It should be noted that the di-primary glycol **13** enters the reaction with thiophenol without catalysts whereas the di-tertiary glycol **16** needs an alkali.[37]

Thus, the interaction of symmetrical and unsymmetrical DA glycols with thiols results in the formation of enyne sulfides containing an alkylthio group in the α-position to the hydroxyl. The addition of thiol follows presumably a regio- and stereoselective fashion, the addition direction being governed by both the triple bond polarity and steric factors. The properties and ^1H NMR spectra of alkylthioenyne glycols **57–79** are presented in Tables VII and VIII.

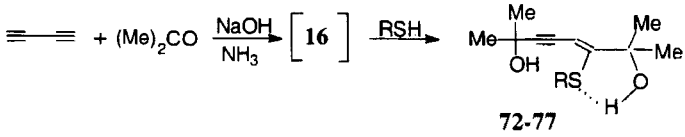
DA condensation with ketones in liquid ammonia looks rather promising in view of its potential use as a side product from acetylene production.[43] A one-pot synthesis of di-tertiary alkylthioenyne glycols

TABLE VII Alkylthioenyne glycols **57–79**[17,37,42,44] 

Compound no.	R^1	R^2	R^3	*Yield*, %	*Boiling point*, °C (mmHg)	*Melting point*, °C	n_D^{20}
57	CH_2OH	CH_2OH	Et	98.0		55	
58	CH_2OH	CH_2OH	*n*-Pr	93.0		46	
59	CH_2OH	CH_2OH	*i*-Pr	91.0		55–57	
60	CH_2OH	CH_2OH	*n*-Bu	95.0		40–42	
61	CH_2OH	CH_2OH	*i*-Bu	94.0	149 (1.5)		1.5634
62	CH_2OH	CH_2OH	*t*-Bu	90.0		59–60	
63	CH_2OH	CH_2OH	C_6H_{13}	97.0		41–43	
64	CH_2OH	CH_2OH	C_8H_{17}	90.0		42–43	
65	CH_2OH	CH_2OH	Et	90.0		92–94	
66	MeCHOH	CH_2OH	Et	35.0	135–136 (3)		1.5650
67	CH_2OH	MeCHOH	Et	50.0	136–137 (3)		1.5637
68	$(Me)_2COH$	CH_2OH	Et	47.0	129–130 (2)		1.5488
69	CH_2OH	$(Me)_2COH$	Et	32.0	128–129 (2)		1.5485
70	$(Me)_2COH$	MeCHOH	Et	48.0	140–141 (3)		1.5438
71	MeCHOH	$(Me)_2COH$	Et	37.0	139–140 (3)		1.5440
72	$(Me)_2COH$	$(Me)_2COH$	Et	96.0		67–68	
73	$(Me)_2COH$	$(Me)_2COH$	*n*-Pr	95.0		38–40	
74	$(Me)_2COH$	$(Me)_2COH$	*i*-Pr	86.0		64–65	
75	$(Me)_2COH$	$(Me)_2COH$	*n*-Bu	89.0	160 (3)		1.5210
76	$(Me)_2COH$	$(Me)_2COH$	*i*-Bu	94.0		46–47	
77	$(Me)_2COH$	$(Me)_2COH$	Ph	95.0		95–97	
78	Et(Me)COH	Et(Me)COH	Et	95.0	152–153 (4)		1.5335
79			Et	94.0	184–186 (4)		1.5668

72–77, based on DA reaction with ketones in the presence of alkaline agents in liquid ammonia, followed by treatment of the reaction mixture with an appropriate thiol, was offered in 1980.[44]

With a DA reagents : ketone : thiol molar ratio of 1 : (2.3–2.7) : (1.1–1.3), in the presence of 0.19–0.27 mol of alkali metal hydroxide, the reaction is directed towards the formation of glycol **16**, whose thiylation leads to the synthesis of glycols **72–77** in 89–90% yield (Scheme 10).



72-77

SCHEME 10

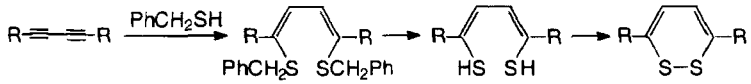
As early as 1967 the addition of benzylthiol to symmetrical disubstituted diynes was shown[12] to proceed regio- and stereoselectively

TABLE VIII ^{1}H NMR spectra of alkylthioenyne glycols **57–79**[17,37]

Compound no.	*CS*, δ, ppm, *CDCl*$_3$							
	SCH$_2$	*CH*$_2$*OH*	*MeCHOH*	*OH*	*=CH*	*Me*	$^4J_{HCH_2}$	$^5J_{HCH_2}$
57	2.91q	4.31d, 4.12s			5.85m	1.21t	~1.2	~2
58	2.90t	4.31d, 4.13s			5.88m	1.00t	~1.2	~2
59		4.31d, 4.10s			5.96m	1.22d	~1.2	~2
60	2.82t	4.33d, 4.17s			5.87m	0.98t	~1.2	~2
61	2.76d	4.32d, 4.15s			5.83m	0.98d	~1.2	~2
62	2.86d	4.32d, 4.16s			5.83m	0.98t	~1.2	~2
63	2.88t	4.30d, 4.13s			5.85m	0.87t	~1.2	~2
64	2.86t	4.30d, 4.14s			5.83m	0.86t	~1.2	~2
65		4.23d, 3.87s			6.02m		~1.2	~2
66	2.93m	4.28d	4.63m		5.98m	1.41d	~1.2	~2
67	2.88m	4.10s	4.41m		5.82m	1.23t	~1.2	~2
68	3.07q	4.32d			6.26t	1.19t	~1.2	
69	2.92q	4.12d			5.82t	1.42t		~2
70	3.05m		4.61m		6.20d	1.25t		
71	2.98m		4.24m		5.97d	1.36s		
						1.50s		
72	3.05q			3.38	6.25s	1.20t		
						1.30s		
						1.40s		
73	3.01t			3.38	6.25s	1.00t		
				3.45		1.32s		
						1.45s		
74					6.28s	1.21d		
						1.32s		
						1.45s		
75	3.05t			3.91	6.25s	1.05t		
				3.45		1.38s		
						1.50s		
76	2.90d			3.75	6.23s	1.00d		
				3.31		1.40s		
						1.52s		
77					6.47s	1.07s		
						1.36q		
78	2.90t			3.35	6.25s	1.20m		
						1.23m		
						1.33m		
						1.40m		
79	33.07q			3.20	6.23s	1.18t		

with the formation of substituted 1,4-(dibenzylthio)-1,3-butadienes[7] of *Z*, *Z*-1,3-configuration.

By means of reductive debenzylation (Na/Liq. NH_3, −70 °C) unsaturated disulfides **80** were converted to *Z*,*Z*-1,3-butadiene-1,4-dithiols **81** which, when exposed to air oxygen or iron chloride in methanol give

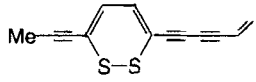


80 **81** **82**

R = H, Me, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$

SCHEME 11

1,2-dithiynes **82** in the form of red crystals. Using the same method unsymmetrical 1,2-dithiynes (R = Ph, 4-MeC_6H_4, H-$MeOC_6H_4$) were obtained.[45] Unstable dithiols **81** were also transformed to diacetates.[46] These data served as the basis in the development of a general synthetic route to 1,2-dithiynes,[47] an interesting class of compounds some of which had been earlier isolated[1] from higher plants (Scheme 11). The addition of thiols to 1,4-disubstituted 1,3-butadiynes occurs at 20 °C in DMF in the presence of catalytic amounts of alkalis to furnish disulfides **80** in a yield approaching 87%. Treatment of the disulfides **80** with lithium amide in THF at −78 °C with subsequent oxidative cycle closing (I_2/KI) leads to the formation of 1,2-ditniynes **82**. From diacetylene glycol **13** a series of 1,2-dithiynes **82** suggested for use as antimycotics, were also prepared.[48] The glycol **13** served as a starting material[7] in the synthesis of thiarubrin A **83**, a potent antibiotic with a wide spectrum of action, previously isolated from *Aspilia africana* leaves.



83

5. CONCLUSIONS

The present review briefly summarizes the advances in the synthesis of hydroxyenyne sulfides, rather promising but still inadequately assessed building blocks and synthons for the synthesis of complex organosulfur molecules including those of natural origin.

Taking into account that the problem of utilization of DA, an unavoidable side product of acetylene industrial synthesis, remains still

unsolved, the data reported in the present review is a timely reminder of the existence of a useful way of comprehensive utilization of DA, that of thiylation with hydrogen sulfide and mercaptans.

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